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Pyrrolidinopiperazinedione as Chiral Auxiliary and its Use in Asymmetric Mannich Synthesis

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Abstract: Functionalised diketopiperazines (DKPs) are easily obtained optically pure by disymmetrization of a mesopyrrolidine and can be easily converted to an α-amino amine containing compound. As a first example, one of the new chiral auxiliaries has been used to prepare an optically pure β-amino ester through a Mannich reaction.
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Diketopiperazines (DKPs) are the smallest and easiest attainable cyclic peptides. The cyclization step which is often the bottleneck of small size cyclic peptide synthesis is in this case highly favoured according to the large entropy gain during the 6 membered-ring formation. Moreover, it is also noteworthy that the DKPs are more stable than the linear peptides and largely represented among natural compounds. Many of them display powerful biological properties. [1]

For these reasons, DKPs, as well as the closely structurally related diketomorpholines have been one of the first class of derivatives to be subjected to the growing field of combinatorial libraries.[2,3] Furthermore DKPs have been used as starting material for the stereoselective synthesis of α-amino acid according to the well-known procedure of Schöllkopf[4] and also as efficient catalysts in asymmetric cyanohydrin synthesis. [5]

In order to develop new synthetic method giving optically pure amines, we have decided to use as a chiral auxiliary a c((D)ProPhe) containing an α-amino amine function (scheme 1) for the following reasons. The amine is located very closely to the bicyclic structure allowing strong interaction between the substrate and the chiral ligand. The c((D)ProPhe) preferentially adopts a folded conformation with the phenyl ring of Phe near by the Hα of Pro. We can expect from these two factors to induce a good diastereoselection. α–Amino amine which is a masked aldehyde would be easily hydrolysed which would simplify the recovering procedure of both the newly formed amine and the DKP auxiliary (scheme 1).

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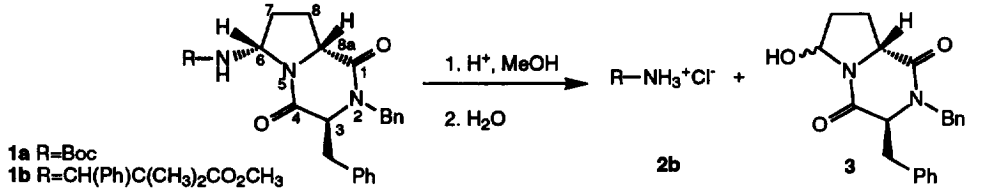
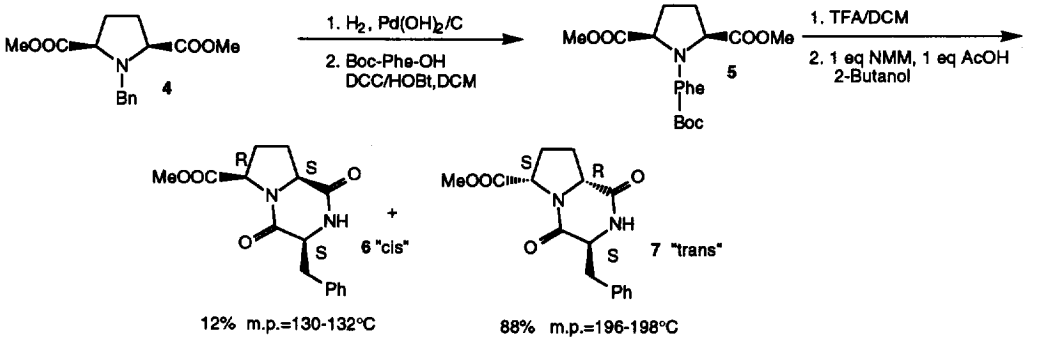


Scheme 1

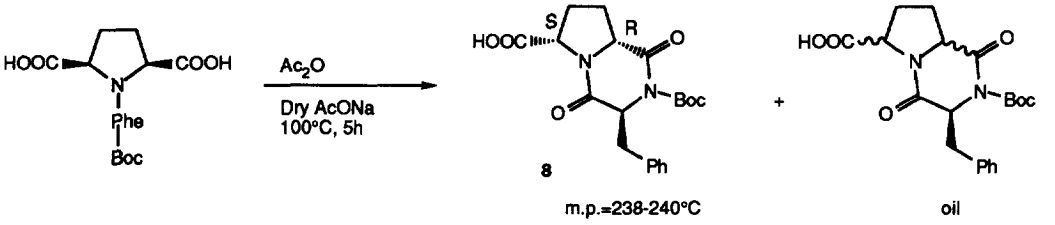
As a first example, we describe here the asymmetric synthesis of β-amino ester **2b** by a Mannich reaction between a ketene alkyl silyl acetal and the imine readily obtained from the new DKP chiral auxiliary **1a** (scheme 5).

Firstly, we report the synthesis of this precursor starting from a readily available meso compound through chemical disymmetrization followed by a smooth Curtius reaction. Meso N-benzyl (2S,5R) dimethoxycarbonyl pyrrolidine **4** readily obtained[6] from cyclisation of N-benzylamine and meso α,α'-dibromodimethyladipate[7] has been debenzylated by catalytic hydrogenation (H_2, 1 atm; $Pd(OH)_2/C$) and coupled to in the presence of DCC-HOBt. The resulting dipeptide **5** obtained in an overall yield of 80% is subjected after Boc-deprotection (TFA-DCM) to cyclisation. This reaction has been performed on the resulting TFA-salt in (+/-)2-butanol containing one equivalent of N-methyl morpholine used as neutralising agent and one equivalent of glacial acetic acid to promote the cyclisation. In these conditions, DKP **7**[8] is obtained in good chemical yield (85%) and diastereomeric excess (76%) (scheme 2) along with a small amount of the diastereomeric DKP **6**.



Scheme 2

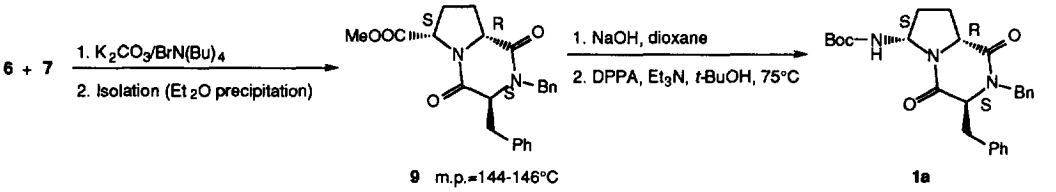
These DKPs have been identified by their ^1H NMR and mass spectra after purification by column chromatography. For the major compound, according to the strong shielding displayed in $CDCl_3$ by the proton on Cα ($\Delta\delta$ppm =1.2) due to the phenyl group folding over the DKP ring already observed for H(Cα) in c((D)ProPhe)[9], it is likely to assume that the same trans configuration occurs in this case. For ascertaining this structural point, X-ray analysis of the structure related and well crystallised DKP **8** have been achieved. The preparation has been done starting after the demethylation (NaOH, dioxane) of compound **5**. The cyclisation step of the resulting diacid is performed in acetic anhydride containing dry sodium acetate.[10] After usual work up, the resulting diastereomeric DKP mixture is composed of a solid product and an oily one easily discarded by ethyl ether extraction (scheme 3). The first one (**8**) has given good monocrystals (from MeOH solution) for X-ray analysis.[11]



Scheme 3

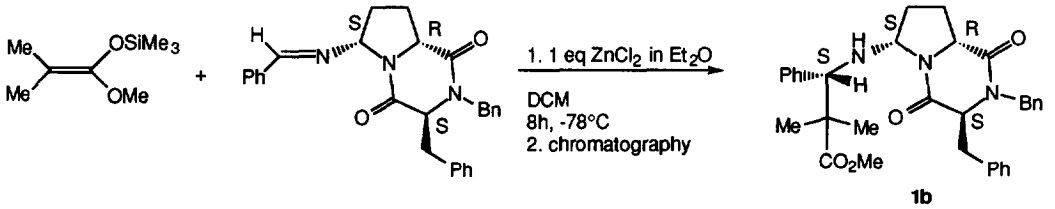
This analysis gives unambiguously the absolute configuration of the three stereogenic centers (3S,6S, 9R). **8** has been further deprotected and methylated ($MeOH/SOCl_2$) to give again DKP **7**.

However, separation of **6** and **7** by column chromatography has shown to be a tedious procedure inefficient for an easy development of a new useful chiral auxiliary. Fortunately we have found that the N-benzyl analogue can be much more easily purified and moreover is much more efficient in the subsequent Curtius reaction step. Therefore, a mixture of **6** and **7** has been subjected to N-benzylation by a phase transfer catalysis (anhydrous K_2CO_3 in anhydrous toluene) as shown in scheme 4. DKP **9** has been isolated in 90% yield just by precipitation in ethyl ether.



Scheme 4

After quantitative ester hydrolysis (NaOH, dioxane, 20°C, 20h), the resulting acid is subjected to a smooth Curtius transformation with 1 eq diphenylphosphoryl azide (DPPA) and 1 eq Et_3N in *t*-BuOH at 75°C during 22h. The resulting compound **1a** is obtained in 85% yield after work up and purification by silica gel chromatography. Boc deprotection (TFA/DCM) leads after TFA evaporation to the TFA amine salt which is immediately coupled with benzaldehyde to form the Schiff base in presence of 1 eq Et_3N and $MgSO_4$ in DCM at 20°C during 2h. This crude imine obtained in a near quantitative yield (95%) after filtration, brine-washing and drying followed by DCM evaporation has been directly subjected to the Mannich reaction[12] (scheme 5).



Scheme 5

The Lewis acid ($ZnCl_2$) is added in dry conditions at -78°C to 1 mole eq of the Schiff base in DCM and stirred during 30 min before adding 1 mole eq of the freshly prepared silylenolether.[13] The reaction is maintained during 8h at -78°C then 12h at -40°C. The medium is hydrolysed at this temperature by careful water addition and usual work up of the reaction has given the crude product in 80% yield. The diastereomeric ratio (12/1) of the adduct was determined by ^1H NMR analysis by integration of the peaks corresponding to the methyl ester groups (δppm 3.68 and 3.65). This adduct can be further purified by column chromatography (silica gel, Et_2O/Hexane: 2/1) giving **1b** in 60% yield. This very good diastereoselectivity can be explained by the formation of a stable complex between the Zn atom and both the imine nitrogen and the well-situated oxygen atom of the pyrrolidino amide group which allows a preferential attack on the Re face of the imine by the entering dimethylketene silyl acetal as already postulated for closely related imine compounds.[14,15]

The target molecule **2b** has been promptly obtained after hydrolysis and characterised as well as the chiral auxiliary moiety **3** which could be easily recycled by standard procedures to give again the protected amine **1a** (scheme 1). Comparison of the optical rotation value of **2b** to that already reported[16] indicates that the (S)-configurated β-amino ester has been obtained after hydrolysis of **1b** with a high enantiomeric purity.

In summary, we have presented here the synthesis of a new chiral auxiliary useful for asymmetric Mannich reaction giving an optically pure β-amino ester. This chiral diketopiperazine is promptly obtained from readily available meso compounds desymmetrized by a cyclisation procedure without any enzymatic step, followed by a smooth Curtius reaction. This first result opens the way for other asymmetric amino transfer reactions using this novel α-amino diketopiperazine.

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11. A crystal of **8** measuring 0.25mm x 0.40mm x 0.40mm was used for X-ray measurements. Crystal data:$C_{20}H_{24}N_2O_6$; orthorhombic, space group $P2_12_12_1$; a = 8.775(2) Å, b = 11.244(2) Å, c=19.658(3) Å, V = 1939(1) $Å^3$, Z = 4, $D_{calcd.}$= 1.330g/cm^3. Intensity measurements were made with $4° < 2\theta < 48°$ by using MoKα radiation (λ = 0.71073Å) at 294 K on an Enraf-Nonius CAD4 diffractometer. A total of 1718 independent reflections were measured, on which 1369 were considered to be observed [| Fo | > σ(Fo)]. The structure was solved by direct methods and refined with SDP software. Refinement of 253 parameters converged at R(F) = 0.40, wR(F) = 0.049, with goodness-of-fit = 1.61.
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16. $[\alpha]_D^{20}$ -35 (*c* 1, 1N HCl); see data in reference 14: $[\alpha]_D^{25}$ -32.8 (*c* 1.1, 1N HCl).

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